Astérisque

A. LASOTA

Ergodic problems in biology

<http://www.numdam.org/item?id=AST_1977__50__239_0>

ERGODIC PROBLEMS IN BIOLOGY

by

A. Lasota

Jagellonian University

1. Introduction. It is obvious that biological systems
are extremely complicated and our methods of measuring bio-
logical parameters are far from to be precise. This is the
usual explanation of the fact that experimental graphs des-
cribing the behavior of biological processes are irregular
and chaotic. The purpose of the present lecture is to give
another (or rather one more) explanation of this phenomenon.
The main idea is to show that in typical biological systems
there exists a continuous (non atomic) invariant measure
such that the corresponding measure theoretical systems are
ergodic, mixing and even exact in the sense of Rohlin.

We start from recalling some recent results concerning
the existence of invariant measures. Then we shall apply
them to the following biological problems:

1) the population growth of a single species,

2) the production of blood cells.

We shall study these problems mainly with the discrete
time using the technique of difference equations. Only in
Section 5 we shall mention some open problems related with
a delay differential equation.

2. **Existence of invariant measures.** Denote by X a topological Hausdorff space. By a measure on X we mean any probabilistic measure defined on the σ-algebra of Borel subsets of X. A measure μ is called continuous if it vanishes on points, that is $\mu(\{x\}) = 0$ for each singleton $\{x\} \subset X$. In [11] and [12] it is proved the following

Theorem 1. Let T: X $\to$ X be a continuous mapping. Assume that there exist two nonempty compact sets A,B $\subset$ X and an integer $n \geqslant 1$ such that

$$T^n(A) \cap T^n(B) \supset A \cup B, \qquad A \cap B = \emptyset .$$

Then there exists on X a continuous measure μ which is invariant and ergodic with respect to T.

In the special case when n = 1 and X is an interval of the real line (X = $\Delta \subset R$), the measure μ may be chosen in such a way that the dynamical system (Δ, μ, T) is isomorphic to the dyadic transformation x $\to$ 2x (mod 1). In this case it is also possible to derive from Theorem 1 the following ([10], [12])

Theorem 2. Let T be a continuous mapping from an interval Δ (boundet or not) into itself. Assume that there exists an integer $n \geqslant 1$ and a point $x_0 \in \Delta$ such that

$$T^{3n}(x_0) = x_0 , \qquad T^n(x_0) \neq x_0 .$$

Then there exists on Δ a continuous measure μ which is invariant and ergodic with respect to T.

From the Birkhoff ergodic individual theorem it follows, immediately, that under conditions of Theorem 2 there exists an uncountable set S ($\mu(S) = 1$) such that each trajectory starting from a point $x \in S$ is simultaneously "turbulent" and "stationary". We call a trajectory $\{T^n(x)\}$ turbulent if its limit set

$$L(x) = \bigcap_{n=1} \text{cl} \left\{ T^n(x), T^{n+1}(x), \ldots \right\}$$

is infinit (In particular it is not a periodic orbit; cf.[20]). A trajectory $\{T^n(x)\}$ is called stationary if for each bounded continuous function f: $\Delta \rightarrow$ R there exists the limit

$$\lim_n \frac{1}{n} \sum_{k=0}^{n-1} f(T^k(x)) .$$

Both properties are essntial from the biological point of view. The first one is responsible for the irregular character of the process under cosideration. The second one enables us to define the time average of each biological parameter related with the process.

Interesting properties of transformations with periodic points of period three were discovered by A.N. Sharkovsky[21] and discussed in several recent papers: [3], [10], [13] and [16]. There remain, however, many open questions. For example, does there exists under assumptions of Theorem 2 a continuous invariant measure μ such that the dynamical system (Δ, μ, T) is exact in the sense of Rohlin [19] ? The problem is of some practical value. An affirmative answer would imply a

highly irregular behavior of trajectories starting from an
uncountable set $S \subset \triangle$.

3. Population growth of a single species. Consider a population with discrete generations. In ideal conditions, when

every individual can mature, the growth of the population
is described by the geometrical progretion $x_{n+1} = \lambda x_n$
where x_n is the number of individuals in the n-th generation
and λ is a constant coefficient larger than 1. In real
conditions most of individuals die before they are able to
create a new generation. This is due to the limitation of
food, existence of compiting species, communicable diseases
and many other factors which became relevant when x_n is large
enough. Thus in the real conditions λ is a decreasing
function of x_n. For the sake of simplicity it is often assu-
med that λ is a linear function, that is: $\lambda = r - qx_n$.
This leads to the recurrence equation $x_{n+1} = (r - qx_n)x_n$.
After changing the variables $u_n = qx_n/r$ we obtain its simpli-
fied form

$$(1) \qquad\qquad u_{n+1} = ru_n(1 - u_n) \ .$$

For $0 \leqslant r \leqslant 4$ the right hand side $T_r(u) = ru(1 - u)$ maps
the unit interval into itself. An easy computation shows
that for $r \geqslant 3.83$ the mapping T_r admits a periodic point of
period three. According to Theorem 2 this implies that, for
$3.83 \leqslant r \leqslant 4$, there exists on $[0,1]$ a continuous measure
which is invariant and ergodic with respect to T_r .

Another, more realistic assumption concerning λ is the

"logistic" formula $\lambda = re^{-qx_n}$. This leads to the equation $x_{n+1} = rx_n e^{-qx_n}$ which after substitution $u_n = qx_n$ may be written as

$$(2) \qquad\qquad u_{n+1} = ru_n e^{-u_n} \; .$$

The right hand side $S_r(u) = rue^{-u}$ maps the half line $[0,\infty)$ into itself and has a periodic point of period three for $r \geqslant 42.8$. Thus for such r's there exists on $[0,\infty)$ a continuous measure which is ergodic and invariant under S_r .

Summarizing our results we conclude that, for r sufficiently large, both systems (1) and (2) describing the population growth of a single species admit an uncountable family of stationary turbulent trajectories. In both cases the biological meaning of the parameter r is the same; it is equal to the maximal (net) reproductive rate. An experimental proof of the chaotic behavior of the size of a population with the high net reproductive rate (insects: lucilla cuprima) was given by A. Nicholson [17] .

Periodic and "chaotic" trajectories of difference equations (1) and (2) have been studied by many authors ; see for example [4],[5],[7],[8],[14],[15] and [22]. In comparison with the previous results which require rather complicated and deep technique, Theorem 2 enables us to predict "stationary turbulence" by solving a simple numerical problem : equation $T^3(u) = u$.

4. **Production of blood cells**. The major blood forming organ is the bone marrow. From the bone marrow the blood

cells pass to the blood vascular system. Here they carry
oxygen from the lungs to the body tissues (red cells) protect
the body against infections (white cells) and participate
in the process of blood clotting (platelets). The blood
cells are not everlasting. After a time they are destroyed
either by the natural aging process or by some accidental
factors (blood diseases, infections,...). An important
property of the bone marrow is the ability to change the
production when the number of blood cells changes.

Denote by x_n the number of blood cells of fixed type
(for example red cells) at time n. We have

$$(3) \qquad x_{n+1} - x_n = - d_n + p_n$$

where d_n is the number of cells which are destroyed in the
time interval $[n,n+1]$ and p_n is the number of cells which
are produced during the same period. We shall assume that
both d_n and p_n are functions of x_n, namely

$$(4) \qquad d_n = \sigma x_n, \qquad p_n = (kx_n)^s e^{-qx}$$

where k,q,s are positive constants and $0 < \sigma < 1$. The first
assumption is quite natural (constant destruction rate) and
the second coincides with recent experimental results due to
Dr. M. Ważewska-Czyżewska. Setting $u_n = qx_n$ and substituting
(4) into (3) we obtain

$$(5) \qquad u_{n+1} = (1 - \sigma)u_n + (cu_n)^s e^{-u} \qquad (c = kq^{\frac{1-s}{s}}) .$$

This simple difference equation enables us to model the behavior of the blood cell population in many clinical cases. We shall show some typical examples without going into biological details. Fix $c = 0.47$, $s = 8$ and consider (5) for a few values of σ.

(a) Normal conditions: $\sigma = 0.1$. Each trajectory $\{u_n\}$ starting with $u_0 \geqslant 2.5$ converges to the stationary solution $\bar{u} = 15.4 \ldots$. If $u_0 \leqslant 2.4$, then $\lim_n u_n = 0$. These facts have a simple biological meaning. In normal conditions the number of blood cells is stable. However, when it is to small (for example after a havy haemorrhage) the organism must die.

(b) Disease: $\sigma = 0.4$. Now there exists the unique periodic solution of period two:

$$\ldots, \quad u_n = 15.5\ldots , \quad u_{n+1} = 10.7\ldots , \quad u_{n+2} = 15.5\ldots ,$$

and any trajectory staring with $u_0 \geqslant 3.4$ is asymptotically periodic. Exceptions are trjectories which finish in the unstable fixed point $\bar{u} = 12.6\ldots$. If $u_0 \leq 3.3$, then $\lim_n u_n = 0$. This behavior of trajectories explains several biological facts first of all the existence of stable oscilations in blood cell population. It is also worthwhile to observe the adoptation of the "ill" system to the new destruction coefficient which now is four times as large. In the case (a) the time average of the number of blood cells was equal to $15.4\ldots$ and now we have

$$\lim_n \frac{1}{n} \sum_{k=0}^{n-1} u_k \quad - \frac{1}{2} (15.5 + 10.7) = 13.1\ldots$$

which is not much worse.

(c) Severe disease: $\sigma = 0.8$. With this value of σ
the right hand side of equation (5)

$$S(u) = (1 - \sigma)u + (cu)^8 e^{-u}$$

maps the interval $[4.2 , 15.1]$ into itself and admits a
periodic point of period three. Thus there exists on this
interval a continuous measure which is ergodic and invariant
with respect to S. This implies the existence of an uncoun-
table family of stationary turbulent trajectories which
remain in the interval $[4.2 , 15.1]$. When $u_0 \leqslant 4.1$, we
have $\lim_n u_n = 0$. There is an experimental evidence of
chaotic oscillations in blood cell populations; see for
example [18]. Equation (5) gives a simple mathematical ex-
planation of this phenomenon.

It is necessary to remark that the model of blood cell
population given by equation (5) is far from to be correct.
The weakness lies in the discretization of time. There is
no biological reason for assuming that the blood is produc-
ted in portions. We can obtain much more realistic model
replacing the difference equation (5) by a similar delay
differential equation. Such equation will be dicussed in the
next Section.

5. Invariant measures for delay differential equations.

Let C_h be the space of continuous functions v: $[-h,0] \to R$
with the supremum norm topology. Consider a functional
differential equation (see: [6])

(6) $\qquad u'(t) = f(u_t) \qquad\qquad 0 \leqslant t < \infty$

where $f: C_h \to R$ is a given function and u_t denotes the res-
triction of the unknown function $u: [-h, \infty) \to R$ to the
interval $[t-h, t]$. We shall suppose that f is sufficiently
regular, for example Lipschitzean

$$|f(v) - f(w)| \leqslant L \|v - w\|_{C_h} \qquad\qquad v, w \in C_h .$$

Then, for each $v \in C_h$. equation (6) admits exactly one solu-
tion $u: [-h, \infty) \to R$ which is continuous on $[-h, \infty)$ differen-
tiable on $[0, \infty)$ and satisfies the initial value condition

(7) $\qquad u(t) = v(t), \qquad\qquad -h \leqslant t \leqslant 0 .$

Given f, consider the mapping $T_f: C_h \to C_h$ defined by the
formula

$$(T_f v)(t) = u(t + h), \qquad\qquad -h \leqslant t \leqslant 0$$

where u is the solution of (6),(7). If f is Lipschitzean,
the mapping T_f is not only uniquely determined on C_h but
also continuous and we can describe the properties of equa-
tion (6) in terms of T_f. Namely, we say that a measure μ on
C_h is invariant (ergodic) with respect to equation (6) if it
is invariant (ergodic) under T_f.

Now we shall show an example of a delay differential
equation for which, as we conjecture, there exists a conti-
nuous ergodic invariant measure. Let us turn back to the
problem of the production of blood cells. Denote by $x(t)$

the number of cells (of fixed type) at time t . We have

(8) $\qquad x'(t) = - d(t) + p(t)$

where $p(t)$ and $d(t)$ denote the instantaneous production and instantaneous destruction at time t respectively. Since the bone marrow needs several days to product a blood cell it is natural to admit that $p(t)$ is a function of $x(t-h)$. Thus instead of (4) we assume that

(9) $\qquad d(t) = - \sigma x(t), \qquad p(t) = (kx(t-h))^s e^{-qx(t-h)}.$

Setting $u = qx$ and substituting (9) into (8) we obtain

(10) $\qquad u'(t) = - \sigma u(t) + (cu(t-h))^s e^{-u(t-h)} .$

Equation (10) with s = 0 was proposed in [23] as a red cell model. In this case (s = 0), according to the recent results of S. N. Chow, J. Mallet-Paret [1],[2] J. Kaplan and J. Yorke [9] it admits periodic solutions for certain values of the parameters h and σ . In the case s $>$ 0 we have the following

Conjecture. For some positive values of the parameters c, h, s and σ there exists on C_h a continuous measure which is ergodic and invariant with respect to equation (10).

Numerical simulations indicate that this is true for c = 0.47 , h = 10 , s = 8 and σ = 0.8 .

For other interesting models of blood cell kinetics and references to the literature consult [18],[23],[24],[25] and [26] .

References

[1] S.N.Chow, Existence of periodic solutions of autonomous functional differential equations,J.Differential Equations 15(1974),350-378.

[2] S.N.Chow and J.Mallet-Paret, Integral averaging and Hopf's bifurcation, preprint, Lefschetz Center for Dynamical Systems.

[3] J.Guckenheimer, On the bifurcation of maps of the interval, Invent. Math. 39(1977),165-178.

[4] J.Guckenheimer, G.Oster and A.Ipaktchi, The dynamics of density dependent population models, J. Math. Biology 4(1977),101-147.

[5] I.Gumowski and C.Mira, Accumulations de bifurcations dans une récurrence, C.R.Acad.Sci.Paris,Sér A-B 281(1975), 45-48.

[6] J.Hale, Functional Differential Equations, Springer Verlag New York 1971.

[7] F.C.Hoppensteadt and J.M.Hyman, Periodic solutions of a logistic difference equation, SIAM J.Appl.Math. 32(1977), 73-81.

[8] M.V.Jacobson, On the properties of the one parameter family of dynamical systems $x \to Axe^{-x}$, Uspehi Mat. Nauk 31(1976),239-240.

[9] J.Kaplan and J.Yorke, On the nonlinear differential delay equation $x'(t) = -f(t,x(t-1))$, J.Differential Equations 23(1977),293-314.

[10] A.Lasota, On mappings isomorphic to r-adic transformations, Ann.Polon.Math.(to appear).

[11] A.Lasota and G.Pianigiani, Invariant measures on topological spaces, Boll.Un.Mat.Ital. 18-B(1977).

[12] A.Lasota and J.Yorke, On the existence of invariant measures for transformations with strictly turbulent trajectories, Bull.Acad.Polon.Sci.Sér.Sci.Math.Astronom.Phys. 25(1977),233-238.

[13] T.Y.Li and J.Yorke, Period three implies chaos, Amer.Math. Monthly 82(1975),985-992.

[14] R.May and G.Oster, Bifurcations and dynamic complexity in simple ecological models, Am.Naturalist 110(1976)573-599.

[15] P.J.Myrberg, Iteration der reellen Polynome zweiten Grades III, Ann.Acad.Sci.Fenn.Ser.A I, 366(1963),1-18.

[16] M.B.Nathanson, Permutations, periodicity and chaos, J.Combinatorial Theory Ser.A 22(1977),61-68.

[17] A.J.Nicholson, An outline of the dynamic of animal populations, Austr.J.Zool. 2(1954),9-65.

[18] J.S.Orr, J.Kirk, K.G.Gray and J.R.Anderson, A study of the interdependence of red cell and bone marrow stem cell populations, Brit.J.Haemat. 15(1968),23-34.

[19] V.A.Rohlin, Exact endomorphisms of Lebesgue spaces, Izv. Akad.Nauk SSSR Ser.Mat. 25(1961),499-530.

[20] D.Ruelle and F.Takens, On the nature of turbulence, Comm. Math.Phys. 20(1971),167-192.

[21] A.N.Sharkovsky, Co-existence of the cycles of continuous mapping of the line into itself, Ukrain.Mat.Z. 16(1964), 61-71.

[22] S.Smale and R.F.Williams, The qualitative analysis of a difference equation of population growth, J.Math.Biology 3(1976),1-5.

[23] M.Ważewska-Czyżewska and A.Lasota, Mathematical models of the red cell system (Polish), Matematyka Stosowana 6(1976),25-40.

[24] G.H.Weiss and G.Zajicek, Kinetics of red blood cells following hemolysis, J.Theoret.Biol. 23(1969),475-491.

[25] T.E.Wheldon, Mathematical models of oscillatory blood cell production, Math.Biosciences 24(1975),289-305.

[26] T.E.Wheldon, J.Kirk and H.M.Finlay, Cyclical granulopoiesis in chronic granulocytic leukemia: a simulation study, Blood 43(1974),379-387.

A. Lasota

Institute of Mathematics

Reymonta 4

Kraków

Poland